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| 09/820,099 | 03/27/2001 | Jan G.J. van de Winkel | MXI-170RCE | 2545 |

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| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |
| ART UNIT | PAPER NUMBER |
| 1643 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/820,099 | VAN DE WINKEL, JAN G.J. | |
| | Examiner | Art Unit | |
| | David J. Blanchard | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 6-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 2-5 and 13-34 are canceled.
Claims 1, 11 and 12 have been amended.
2. Claims 1 and 6-12 are pending and under consideration.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. This Office Action contains New Grounds of Rejections.

### *Objections/Rejections Withdrawn*

5. The objection to claim 34 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of the cancellation of the claim.
6. The objection to the specification as failing to provide proper antecedent basis for the term "non-natural recombinant genetic fusion" is withdrawn in view of the cancellation of claim 34.
7. The rejection of claims 1, 6-12 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is withdrawn in view of the cancellation of claim 34 and the amendments to the claims and in view of the new grounds of rejections below.
8. The rejection of claims 1 and 6-12 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric (serum) IgA or administering a bispecific antibody comprising an antibody fragment that binds Fc$\alpha$RI outside the natural ligand binding domain and an antibody fragment that binds a target cell or antigen, wherein the antibody fragments of the bispecific antibody are linked via chemical conjugation or by recombinant genetic fusion, does not reasonably provide enablement for a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric IgA linked via chemical conjugation or recombinant genetic fusion to a second agent that binds a

target cell or antigen as embraced by the claims is withdrawn in view of the amendments to the claims and in view of the new grounds of rejections below.

9. The rejection of claim 34 is rejected under 35 U.S.C. 102(b) as being anticipated by van Spriel et al (Journal of Infectious Diseases, 179(3):661-669, 1999, first publicly available date of 3/3/1999) is withdrawn in view of the cancellation of the claim.

10. The rejection of claim 34 is rejected under 35 U.S.C. 102(e) as being anticipated by Deo et al (US Patent 5,922,845, filed 7/11/1996, cited on PTO-892 mailed 1/26/2006) is withdrawn in view of the cancellation of the claim.

***New Grounds of Rejections***

11. Claims 1 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 6/13/2007 has introduced NEW MATTER into the claims. As presently amended the claims are drawn to a method for eliminating a target cell or antigen from the circulatory system of a subject comprising administering to the subject a composition comprising monomeric IgA that binds to FcαRI and an agent which specifically binds to the target cell or antigen, wherein the agent comprises an antibody or an antibody fragment thereof, wherein the target cell is a cancer cell and the target antigen is a bacteria, a virus or a fungus and the method further comprises administering a cytokine selected from GM-CSF, IL-6, IL1β, IL-8 and TNF-α and wherein the composition is administered by injection or intravenously. Thus, the claim encompass methods of treating cancer, or treating bacterial, viral and fungal infections in a subject comprising administering monomeric IgA and an antibody or antibody fragment thereof (i.e., agent) which specifically binds to the target cell, i.e., cancer cell

or a bacterial, viral or fungal antigen. The reply filed 6/13/2007 states that support can be found at least at pg. 2, lines 27-33; pg. 3, lines 12-18, 33-37; pg. 8, lines 14-20; pg. 13, lines 8-14; pg. 14, lines 26-30 and pg. 25, lines 6-8.

Page. 2, lines 27-33 disclose:

Accordingly, in one embodiment, the invention provides a method for eliminating a target cell or antigen from the circulatory system (i.e., the portal circulation) of a subject by administering to the subject a composition (e.g., a molecular complex) comprising a first portion which specifically binds FcαRI expressed on liver Kupffer cells, or which specifically binds monomeric IgA or the Fc region thereof (which, in turn, binds FcαRI), linked to a second portion which specifically binds the target cell or antigen.

Page 3, lines 12-18 disclose:

The compositions of the present invention can be used to prevent entry of, or eliminate harmful pathogens (e.g., bacteria, viruses, fungi, tumorous cells etc.) from circulation by targeting these pathogens to FcαR-expressing effector cells at the interface (e.g., barrier) of the mucosal and systemic immune systems. In particular, these pathogens can be targeted to FcαR-expressing Kupffer cells in the sinusoid of the liver which, when bound by the complexes of the invention, mediate phagocytosis of the pathogens.

Page 3, lines 33-37 disclose:

In a further aspect, the invention includes a method for treating or preventing septicemia, characterized, for example, by a defective mucosal barrier and concomitantly produced inflammatory mediators, in a subject by administering to the subject a composition (e.g., a molecular complex) of the invention which targets a bacterium, fungus or virus to FcαRI-expressing liver cells.

Page 8, lines 14-20 discloses:

In one in one embodiment, me invention provides a method for eliminating a target cell or antigen from the circulatory system (i.e., the portal circulation) of a subject by administering to the subject a composition (e.g., a molecular complex) comprising a first portion which specifically binds FcαRI expressed on liver Kupffer cells, or which specifically binds monomeric IgA or the Fc region thereof (which, in turn, binds FcαRI), linked to a second portion which specifically binds the target cell or antigen.

Page 13, lines 8-14 discloses:

The compositions of the present invention can be used to prevent entry of, or eliminate harmful pathogens (e.g., bacteria, viruses, fungi, tumorous cells etc.) from circulation by targeting these pathogens to FcαR-expressing effector cells at the interface (e.g., barrier) of the mucosal and systemic immune systems. In particular, these pathogens can be targeted to FcαR-expressing Kupffer cells in the sinusoid of the liver which, when bound by the complexes of the invention, mediate phagocytosis of the pathogens.

Page 14, lines 26-30 discloses

In another embodiment, the complexes are used to treat or prevent septicemia characterized, for example, by a defective mucosal barrier and concomitantly produced inflammatory mediators, in a subject by administering to the subject a composition (e.g., a molecular complex) of the invention which targets a bacterium, fungus or virus to FcαRI-expressing liver cells.

Applicant's invention is based on the discovery (which may or may not be novel and non-obvious, particularly in view of the prior art currently of record) that monomeric IgA-antigen complexes are efficiently phagocytosed by FcαR-expressing cells (i.e., Kupffer cells), whereas secretory (dimeric) IgA does not initiate phagocytosis. As noted by the examiner in the previous Office Action, the specification as filed appears to provide adequate written description for (i) the administration of serum IgA (monomeric), *but not linked by chemical conjugation or recombinant genetic fusion* to an agent or antibody that binds a target cell or antigen and causes the elimination of said target cell or antigen and (ii) bispecific antibodies that bind "outside the natural ligand binding domain of the trigger receptor" (specification at pg. 9, lines 19-20) to circumvent interference by serum antibodies, wherein the linkage of the two binding components (i.e., Fab) of the bispecific antibody are linked by chemical conjugation or recombinant genetic fusion. The as filed specification as pointed to by Applicant does not provide adequate written support for a method of treating cancer, or treating bacterial, viral and fungal infections comprising administering monomeric IgA and an antibody or antibody

fragment thereof (i.e., agent) which specifically binds to the target cell, i.e., cancer cell or a bacterial, viral or fungal antigen. The as filed disclosure as pointed to by applicant does not disclose a composition comprising monomeric IgA and an antibody or antigen-binding fragment thereof that binds a cancer cell or a bacterial, viral or fungal antigen for the elimination of the cancer cell, or bacterial, viral or fungal infection. Further, the specification does not disclose that the antibody or antibody fragment which binds cancer cell or a bacterial, viral or fungal antigen targets the cancer cell, bacteria, virus or fungus to FcαRI-expressing liver cells. The as filed specification discloses that it is the Fc region of monomeric IgA that interacts with FcαRI expressed on liver Kupffer cells and causes elimination (e.g., phagocytosis) of monomeric IgA-antigen complexes. The specification does not disclose the elimination of "an agent" which is an antibody or antibody fragment thereof which is claimed to specifically bind the target cell or antigen, not monomeric IgA.

As presently amended, the claims now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in the presently amended claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in the present claims in the specification or claims, as filed, or remove these limitations from the claims in response to this Office Action.

12. Claims 1 and 6-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric (serum) IgA or administering a bispecific antibody comprising an antibody fragment that binds FcαRI outside the natural ligand binding domain and an antibody fragment that binds a target cell or antigen, wherein the antibody fragments of the bispecific antibody

are linked via chemical conjugation or by recombinant genetic fusion, does not reasonably provide enablement for a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric IgA and an agent/antibody/antibody fragment that binds a target cell or antigen as embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of eliminating a target cell or antigen from the circulatory system of a subject comprising administering monomeric IgA and an agent that binds a target cell or antigen wherein the agent is an antibody or antibody fragment thereof and the target cell is a cancer cell or the antigen is a bacterial, viral or fungal antigen. Thus, the claims encompass the administration of monomeric IgA and an antibody or antibody fragment (i.e., "agent") that binds a target cell or antigen for the elimination of the cancer cell, or bacterial, viral or fungal infection.

The specification does not provide a sufficiently enabling description of the claimed invention. The specification teaches that the administration of serum IgA (monomeric) complexed, *but not linked by chemical conjugation or recombinant genetic fusion*, with antigen as causing the elimination of antigens bound to monomeric IgA and (b) bispecific antibodies that bind "outside the natural ligand binding domain of the trigger receptor" (specification at pg. 9, lines 19-20) to circumvent interference by serum

antibodies, wherein the two binding components (i.e., Fab) of the bispecific antibody are linked by chemical conjugation or recombinant genetic fusion. The specification also teaches that tumor specific mAb of human IgA class are not available and serum IgA may interfere with the activity of IgA mAbs under physiological conditions (pg. 9). The specification teaches that dimeric IgA (SIgA) was unable to initiate phagocytosis (see pg. 8). The specification does not teach a method of eliminating a target cell or antigen, inclusive to a cancer cell, a bacterial, viral or fungal antigen comprising administering monomeric IgA that binds to FcαRI and an agent or antibody that binds said target cell or antigen. There are no working examples of a method of eliminating a target cell or antigen, inclusive to a cancer cell, a bacterial, viral or fungal antigen comprising administering monomeric IgA that binds to FcαRI and an agent or antibody that binds said target cell or antigen. Thus, the scope of the claims is broad relative the enablement of the present application. The scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

The state of the prior art is such that a single class of IgA FcR binds to monomeric IgA, known as FcαRI or CD89. FcαRI binds both antigen-complexed and monomeric IgA1 and IgA2, and cross-linking of FcαRI on myeloid effector cells by polymeric IgA, IgA immune complexes, or mAbs specific for epitopes within or outside the ligand-binding domain stimulates degranulation, superoxide release, secretion of inflammatory cytokines, endocytosis and phagocytosis. (Deo et al, The Journal of immunology, 160:1677-1686, 1998, IDS reference field 1/22/2002). Neither applicant nor the relevant art at the time of filing teach the administration of monomeric IgA that binds FcαRI and an antibody or antibody fragment thereof (i.e., "agent") wherein the antibody or antibody fragment thereof binds the target cell or antigen thereby eliminating the target cell or antigen from the circulatory system. Applicant has not provided any guidance or direction to assist those skilled in the art in practicing the claimed invention, particularly how the administration of an antibody or antibody fragment thereof that binds a target cell or antigen eliminates that target cell or antigen from the circulatory

system of a subject. Applicants' disclosure as well as the prior art of Deo et al (supra) teach that antigen-complexed monomeric IgA binds FcαRI thereby initiating FcαRI-mediated phagocytosis and hence, elimination of the target cell or antigen from the circulatory system of the subject. The is insufficient evidence or nexus between the administration of an antibody or antibody fragment thereof that binds a target cell or antigen and mediates the elimination of the target cell or antigen by initiating FcαRI-mediated phagocytosis, since it is monomeric IgA which binds FcαRI thereby initiating FcαRI-mediated phagocytosis. There is insufficient guidance and direction to assist those skilled in the art in practicing the claimed invention comprising administering monomeric IgA and an antibody or antibody fragment thereof that binds a target cell or antigen for eliminating a target cell or antigen from the circulatory system of a subject. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).

One of skill in the art would neither expect nor predict the appropriate functioning of the claimed composition comprising monomeric IgA and an antibody or antibody fragment thereof that binds a target cell or antigen as broadly as is claimed.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Deo et al, the lack of guidance and direction provided by applicant, and lack of working examples of a composition comprising monomeric IgA and an antibody or antibody fragment thereof that binds a target cell or antigen for eliminating the target cell or antigen from the circulatory system of a subject, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods, commensurate in scope with the claimed invention.

13. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643